Hodgkin Lymphoma

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Hodgkin Lymphoma

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Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one tumor paraffin block. Re-biopsy if consult material is non-diagnostic. Core needle biopsy may be adequate if diagnostic, but an excisional nodal biopsy is recommended.
- FNA alone is insufficient
- Adequate immunophenotype to confirm diagnosis
  - Immunohistochemistry on paraffin panel for Hodgkin lymphoma (HL) including nodular lymphocyte predominant HL:
    - CD20, PAX-5, CD30, CD3, CD15, CD21, and CD45 (LCA)
    - In situ hybridization for Epstein-Barr encoding region (EBER)

OF USE IN CERTAIN CIRCUMSTANCES:

- Immunohistochemical studies:
  - LMP1
  - BOB1, OCT2, and CD79a (differential diagnosis with mediastinal gray zone lymphoma and primary mediastinal large B-cell lymphoma).
  - CD23, or CD35 (follicular dendritic cell markers), BCL6 in cases of nodular lymphocyte predominant HL (may help with T-cell/ histiocyte rich large B-cell lymphoma)
  - CD2, CD43, ALK (differential diagnosis with anaplastic large cell lymphoma)

STRONGLY RECOMMEND:

- Core biopsy for tissue banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- History and physical including:
  - Alcohol intolerance
  - Pruritus
  - Exam of nodes
  - B symptoms (unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10% of body weight ≤ 6 months of diagnosis)
  - Performance Status
  - Fatigue
  - Size of spleen, liver
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, calcium, uric acid
- Erythrocyte sedimentation rate (ESR)
- Screening for HIV 1, HIV 2, hepatitis B and C (HBcAb, HBsAg, HCVAb) (refer to Hepatitis B Virus (HBV) Screening and Management and Hepatitis C Virus (HCV) Screening algorithms)
- PET/CT with contrast
- Pulmonary Function Tests
- Consider bone marrow biopsy if there are cytopenias and/or inconclusive PET
- MUGA scan or echocardiogram
- Counseling: psychosocial if clinically indicated
- Lifestyle risk assessment[1]
- Discuss fertility options and sperm banking for patients of child bearing potential (refer to Fertility Preservation Prior to Cancer Treatment algorithm)
- Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[2]

OF USE IN SELECTED CASES:

- Chest x-ray, PA and LAT
- Pregnancy test
- Cardiology consultation at baseline if risk factors for cardiac toxicity [*e.g.,* obesity, abnormal echocardiogram, hypertension (HTN), hyperlipidemia (HLD)]

See Pages 3-4: Classic Hodgkin Lymphoma Stage I-II

See Page 5: Classic Hodgkin Lymphoma Advanced Stages III, IV

See Page 6: Lymphocyte Predominant Hodgkin Lymphoma

[1] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

[2] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

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Hodgkin Lymphoma

Classic Hodgkin Lymphoma Stage I-II Combined Modality Therapy

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Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION | **PRIMARY TREATMENT** | **RESPONSE EVALUATION** | **TREATMENT**

Classic Hodgkin Lymphoma Stage I-II with preference to treat with combined modality therapy

Favorable per GHSG[1]?

Yes

ABVD for 2 cycles → PET/CT

- Deauville/5PS[2] 1-3 → ISRT[3] → See Page 7: Follow-up After Completion of Treatment
- Deauville/5PS[2] 4[4] → ABVD for 2 cycles followed by PET/CT → Complete response[5]? **Yes** → ISRT[3] → See Page 7: Follow-up After Completion of Treatment; **No** → Biopsy → Biopsy negative? **Yes** → • Multidisciplinary conference with disease site specialist • Excisional biopsy if available; **No** → See Page 8: Salvage Therapy
- Deauville/5PS[2] 5 → Biopsy → Biopsy negative? **Yes** → • Multidisciplinary conference with disease site specialist • Excisional biopsy if available; **No** → See Page 8: Salvage Therapy

No

ABVD for 2 cycles → PET/CT

- Deauville/5PS[2] 1-3 → • ABVD for 2 cycles with ISRT[3] **or** • AVD for 4 cycles with or without ISRT[3] → See Page 7: Follow-up After Completion of Treatment
- Deauville/5PS[2] 4 → ABVD for 2 cycles followed by PET/CT → Complete response[5]? **Yes** → ISRT[3] → See Page 7: Follow-up After Completion of Treatment; **No** → Biopsy → Biopsy negative? **Yes** → • Multidisciplinary conference with disease site specialist • Excisional biopsy if available; **No** → See Page 8: Salvage Therapy
- Deauville/5PS[2] 5 → Biopsy → Biopsy negative? **Yes** → • Multidisciplinary conference with disease site specialist • Excisional biopsy if available; **No** → See Page 8: Salvage Therapy

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
ISRT = involved site radiation therapy
GHSG = German Hodgkin Study Group

[1] See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
[2] See Appendix B: Deauville Criteria/5-Point Scale (5PS)
[3] See Appendix C: Radiation Therapy Guidelines
[4] Consider multidisciplinary conference with disease site specialist
[5] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

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Hodgkin Lymphoma

Classic Hodgkin Lymphoma Stage I-II Chemotherapy Alone

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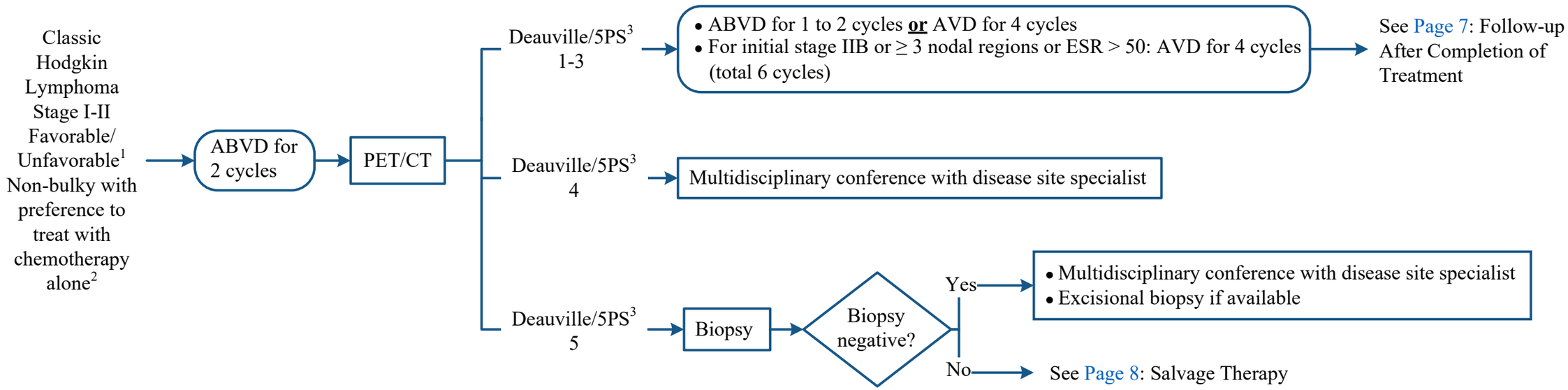
Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION | **PRIMARY TREATMENT** | **RESPONSE EVALUATION** | **TREATMENT**



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine

[1] See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
[2] A subset of patients who meet criteria as per the UK Rapid study with stage IA and stage IIA Hodgkin Lymphoma with no mediastinal bulk and negative PET findings after treatment may receive 3 cycles of chemotherapy with or without additional involved site radiation therapy (ISRT)
[3] See Appendix B: Deauville Criteria/5-Point Scale (5PS)

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Hodgkin Lymphoma

Classic Hodgkin Lymphoma Advanced Stages III, IV

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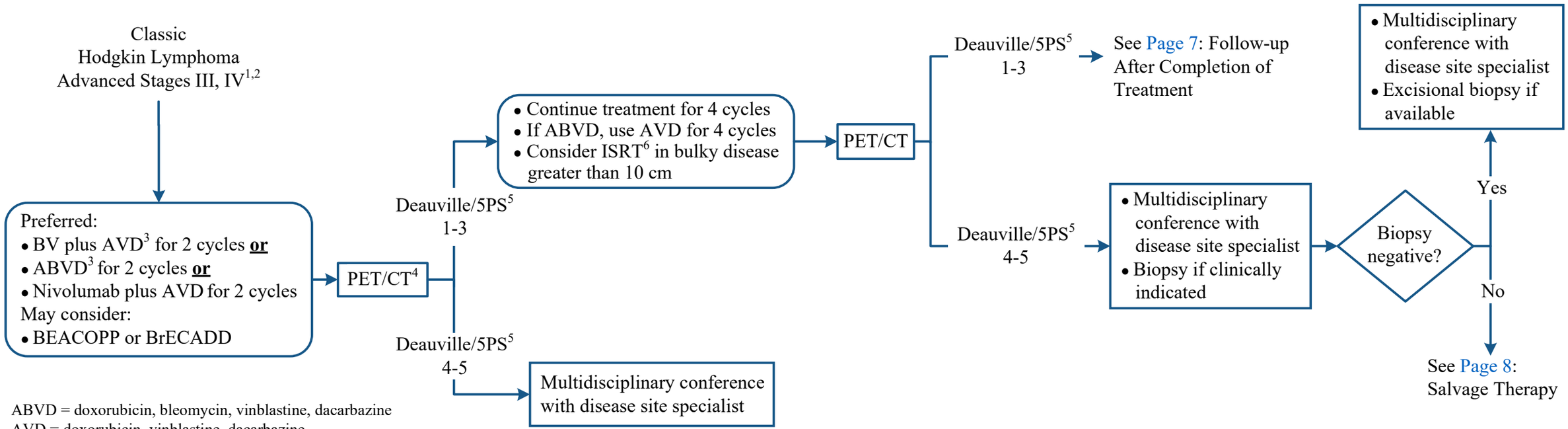
Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION/ PRIMARY TREATMENT | **INITIAL RESPONSE EVALUATION** | **TREATMENT** | **RESPONSE EVALUATION/FOLLOW UP**



ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
BEACOPP = bleomycin. etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine. prednisone
BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone
BV = brentuximab vedotin
ISRT = involved site radiation therapy

[1] Advanced stage is consistent with an International Prognostic Score (IPS) ≥ 4, age < 60 years [see Appendix D: International Prognostic Score (Hasenclever Index)]
[2] Choice of regimen is based on IPS, comorbidities and physician discretion
[3] Patients with IPS ≥ 4 (see Appendix D) and age < 65 years may benefit from BV plus AVD. Contraindicated in patients with Grade 2 or higher neuropathy. Patients who are at higher risk for bleomycin lung toxicity should be considered for BV plus AVD.
[4] BV plus AVD and nivolumab plus AVD are not PET adapted
[5] See Appendix B: Deauville Criteria/5-Point Scale (5PS)
[6] ISRT may be considered depending on location and extent of disease and with expert multidisciplinary discussion with Medical and Radiation Oncology. See Appendix C: Radiation Therapy Guideline

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Hodgkin Lymphoma

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

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Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION | **PRIMARY TREATMENT** | **INITIAL RESPONSE EVALUATION**

NLPHL
Stages IA, IIA (non-bulky)

- ISRT[1] (preferred for stage IA or continguous stage IIA)

or

- Observe if excisional biopsy with no residual disease

NLPHL
Stages IB, IIB
or
Stage 1A (bulky)/Stage IIA (bulky or non-contigous)

- Systemic therapy (rituximab or R-CHOP) with consideration for ISRT[1]

or

- ISRT[1] alone maybe be appropriate in certain circumstances

NLPHL
Stages III, IV

- Observe if asymptomatic and low disease burden

or

- Systemic therapy (rituximab or R-CHOP) with or without ISRT[1]

or

- Palliative radiation of locally symptomatic disease

PET/CT negative?

Yes → Observe → See Page 7: Follow-up After Completion of Treatment

No → Biopsy → Biopsy negative?

Yes →
- Multidisciplinary conference with disease site specialist
- Excisional biopsy if available

No → See Page 8: Salvage Therapy

ISRT = involved site radiation therapy
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

[1] See Appendix C: Radiation Therapy Guideline

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Note: Consider Clinical Trials as treatment options for eligible patients.

FOLLOW-UP AFTER COMPLETION OF TREATMENT

- Follow-up with an oncologist is recommended
- Interim history and physical: every 3 months for first year, then, then every 6 months until year 3, then annually
- Pneumococcal and meningococcal revaccination if patient treated with splenic radiation therapy. See Management of Adult Asplenic/Hyposplenic Patients algorithm.
- Annual influenza vaccine (especially if patient treated with bleomycin or chest radiation therapy)
- Laboratory studies:
  - CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, calcium, every 3 months for first year, then every 6 months until year 3, then annually
  - TSH every 6-12 months if radiation therapy to thyroid and optional for all other cases
- CT neck, chest, abdomen and pelvis with contrast every 3-6 months for 2 years as clinically indicated; then after 2 years as indicated for suspected relapse. PET/CT only if last PET was Deauville/5PS 4-5, to confirm complete response.
- Annual breast screening: If prior thoracic radiation therapy, initiate breast screening 8 years post therapy or at age 40 years, whichever is sooner. If radiation therapy was given between the ages of 10 and 30 years, annual bilateral MRI breast with and without contrast should be performed in addition to annual screening mammography. Refer to Breast Cancer Screening algorithm.
- Counseling: reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion
- Recommend written follow-up instructions for the patient
- Cardiovascular risk assessment (refer to Survivorship – Adult Cardiovascular Screening algorithm)
  - Echocardiogram every 5 years after treatment is completed
  - Stress test at 10 years after treatment is completed, then every 5 years
  - Consider baseline carotid ultrasound after treatment is completed if neck irradiation with follow up ultrasound every 5 years if normal. If abnormal, obtain every 6-12 months as indicated.
- Refer to Survivorship – Hodgkin Lymphoma algorithm for patients 2 years post-treatment and no evidence of disease (NED)

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Hodgkin Lymphoma

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Note: Consider Clinical Trials as treatment options for eligible patients.

SALVAGE THERAPY

Relapse or Refractory disease

- Systemic therapy for relapse or refractory disease (see Appendix E) followed by PET/CT
- Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[1]

Complete response[2]

- AHSCT[3,4] with or without locoregional radiation therapy
- Consider maintenance therapy with novel therapy (BV or PD1 checkpoint inhibitor or combination) for patients with primary refractory disease **or** any of the following risk factors:
  - Early relapse < 12 months
  - Extranodal disease[5] at time of relapse
  - Not in CR at time of AHSCT
  - B symptoms[6]
  - Greater than 1 salvage/subsequent therapy regimen

RESPONSE EVALUATION

Progressive disease post AHSCT?

Yes

- See Appendix E: Systemic Therapy for Relapse or Refractory Disease **or**
- Consider allogenic stem cell transplant **or**
- Clinical or CAR T-cell therapy trial **or**
- Consider clinical trial

No

See Page 7: Follow-up After Completion of Treatment

Partial response[2]

Consider changing to different regimen[7]

Complete response or near complete response[2]?

Yes

No

- Consider gemcitabine-based chemotherapy[7] **or**
- Immunotherapy[7] **or**
- Other cellular therapies if not previously given **or**
- Clinical trial

AHSCT = autologous hematopoietic stem cell transplant
BV = brentuximab vedotin
CAR = chimeric antigen receptor

[1] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

[2] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

[3] Conventional-dose chemotherapy may precede high-dose therapy. Sequence of therapy may vary.

[4] Perform biopsy if plan to treat with high-dose chemotherapy

[5] Extranodal disease (*i.e.*, any tumor spread that involves tissues other than those of the lymph nodes, spleen, thymus, Waldeyer's tonsillar ring, appendix, and Peyer's patches)

[6] Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis

[7] See Appendix E: Systemic Therapy for Relapse or Refractory Disease

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APPENDIX A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma

Risk Factor	GHSG	EORTC	NCCN
Age		≥ 50	
Histology			
ESR and B symptoms[1]	ESR > 50 mm/hour if A; ESR > 30 mm/hour if B	ESR > 50 mm/hour if A; ESR > 30 mm/hour if B	ESR ≥ 50 mm/hour **or** any B symptoms[1]
Mediastinal mass	MMR > 0.33	MTR > 0.35	MMR > 0.33
# Nodal sites	Area ≥ 3^2	Sites > 3^2	Sites > 3
E lesion	any		
Bulky[3]			Size > 10 cm

A = no B symptoms
GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6
NCCN = National Comprehensive Cancer Network

[1] Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis
[2] The EORTC includes the infraclavicular/subpectoral area with the axilla area while the GHSG includes this area with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.
[3] Bulky may be defined as MMR > 0.33 **or** any mass >10 cm in size

APPENDIX B: Deauville Criteria/5-Point Scale (5PS)

- Score 1: no uptake
- Score 2: uptake less than or equal to mediastinum
- Score 3: uptake greater than mediastinum but less than or equal to liver
- Score 4: uptake moderately greater than liver
- Score 5: uptake markedly greater than liver and/or new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

A Deauville Criteria/5PS score of 1-3 is regarded as negative and 4 or 5 as positive

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APPENDIX C: Radiation Therapy Guidelines

Consider intensity-modulated radiation therapy (IMRT) or proton therapy, as appropriate, to minimize toxicity

Dose if radiation therapy is given alone:
30-45 Gy, depending on treatment intent, disease bulk, *etc.*

Doses for combined modality radiation therapy:
- Early stage favorable: 20 Gy to involved site
- Early stage unfavorable: 30 Gy to involved site

Salvage radiation therapy when Deauville/5PS ≥ 4[1]:
36-45 Gy, depending on disease bulk and response to chemotherapy

Radiation Fields:
Involved Site Radiation Therapy: Treatment of involved lymph nodes regions only

[1] See Appendix B: Deauville Criteria/5-Point Scale (5PS)

APPENDIX D: International Prognostic Score (Hasenclever Index[1])

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 years
- Stage IV disease
- White blood cell count ≥ 15 K/microliter
- Lymphocyte count < 8% of white blood cell count, and/or lymphocyte count < 0.6 K/microliter)

Each factor = 1 point

[1] Hasenclever, D., Diehl, V., Armitage, J. O., Assouline, D., Björkholm, M., Brusamolino, E., … Eghbali, H. (1998). A prognostic score for advanced Hodgkin's disease. *New England Journal of Medicine, 339*(21), 1506-1514. doi:10.1056/NEJM199811193392104

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APPENDIX E: Systemic Therapy for Relapsed or Refractory Disease

Disease	Systemic Therapy Options	Subsequent Options[1]
Classic Hodgkin Lymphoma	• Brentuximab vedotin • Brentuximab vedotin plus bendamustine • Brentuximab vedotin plus nivolumab • Brentuximab vedotin plus ICE (ifosfamide, carboplatin, etoposide) • DHAP (dexamethasone, cisplatin, high dose cytarabine) • ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin) • Gemcitabine/bendamustine/vinorelbine • GVD (gemcitabine, vinorelbine, liposomal doxorubicin) • ICE (ifosfamide, carboplatin, etoposide) • IGEV (ifosfamide, gemcitabine, vinorelbine) • Pembrolizumab plus GVD (gemcitabine, vinorelbine, liposomal doxorubicin) • Pembrolizumab for patients not eligible for stem cell transplant • Pembrolizumab plus ICE (ifosfamide, carboplatin, etoposide) • Nivolumab plus ICE (ifosfamide, carboplatin, etoposide)	• Bendamustine • Bendamustine plus carboplatin plus etoposide • Everolimus • GCD (gemcitabine, carboplatin, dexamethasone) • Lenalidomide • Nivolumab • Pembrolizumab • GEMOX (gemcitabine plus oxaliplatin) • Vinblastine
Lymphocyte Predominant Hodgkin Lymphoma	• Rituximab plus DHAP (dexamethasone, cisplatin, high dose cytarabine) • Rituximab plus ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin) • Rituximab plus ICE (ifosfamide, carboplatin, etoposide) • Rituximab plus IGEV (ifosfamide, gemcitabine, vinorelbine)	

[1] Subsequent options also include systemic therapy options that were not previously given

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